



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125597/0

BLA APPROVAL

Pax Vax Bermuda Ltd.
Attention: Mr. Mark Meltz
Clarendon House
2 Church Street
Hamilton, Bermuda HM 11

June 10, 2016

Dear Mr. Meltz:

Please refer to your Biologics License Application (BLA) for Cholera Vaccine, Live, Oral dated October 16, 2015, submitted under section 351(a) of the Public Health Service Act (PHS Act).

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2041 to PaxVax Bermuda Ltd, Hamilton, Bermuda under the provisions of section 351(a) of the PHS Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Cholera Vaccine, Live, Oral, which is indicated for active immunization against disease caused by *Vibrio cholerae* serogroup O1. Cholera Vaccine, Live, Oral is approved for use in adults 18 through 64 years of age traveling to cholera-affected areas.

The review of this product was associated with the following National Clinical Trial (NCT) number(s): NCT01585181, NCT01895855, NCT02094586 and NCT02100631.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Cholera Vaccine, Live, Oral intermediate bulk drug substance at [REDACTED]

[REDACTED] The intermediate bulk drug substance will be processed to drug substance at PaxVax, Inc. [REDACTED] The final formulated active component of the vaccine will be manufactured, filled, labeled and primary-packaged at PaxVax, Inc. [REDACTED] The bulk buffer component of the vaccine will be manufactured at [REDACTED] and filled and primary-packaged at PaxVax, Inc. [REDACTED] The active component and the buffer component will be secondary-packaged together at [REDACTED]

You may label your product with the proprietary name VAXCHORA and market it in single dose cartons containing a buffer component packet and an active component packet.

We did not refer your application to the Vaccines and Related Biological Products Advisory Committee because our review of information submitted in your BLA, including the clinical study design and trial results, did not raise concerns or controversial issues that would have benefited from an advisory committee discussion. In addition, on May 27, 1998, an advisory committee meeting was held to discuss approaches to demonstrate effectiveness of a live oral cholera vaccine for travelers; advice from this committee was considered in the review of this application.

DATING PERIOD

The dating period for the active component packet of Cholera Vaccine, Live, Oral shall be 18 months from the date of manufacture when stored at -25°C to -15°C. The dating period for the buffer component packet shall be 24 months from the date of manufacture when stored at -25°C to -15°C. The date of manufacture shall be defined as the date of initiation of filling into final container. The expiration date for the packaged final drug product, containing one active component packet and one buffer component packet shall be dependent on the shortest expiration date of any component.

FDA LOT RELEASE

Please submit final container samples of the product in final containers together with protocols showing results of all applicable tests. You may not distribute any lots of product until you receive a notification of release from the Director, Center for Biologics Evaluation and Research (CBER).

BIOLOGICAL PRODUCT DEVIATIONS

You must submit reports of biological product deviations under 21 CFR 600.14. You should identify and investigate all manufacturing deviations promptly, including those associated with processing, testing, packaging, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to the Director, Office of Compliance and Biologics Quality, at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

MANUFACTURING CHANGES

You must submit information to your BLA for our review and written approval under 21 CFR 601.12 for any changes in, including but not limited to, the manufacturing, testing, packaging or labeling of Cholera Vaccine, Live, Oral, or in the manufacturing facilities.

LABELING

We hereby approve the draft package insert labeling submitted under amendment# 49, dated June 10, 2016 and the draft carton and container labeling submitted under amendment# 50, dated June 10, 2016.

Please provide your final content of labeling in Structured Product Labeling (SPL) format and include the carton and container labels. In addition, please submit three original paper copies for carton and container final printed labeling. All final labeling should be submitted as Product Correspondence to this BLA 125597/0 at the time of use (prior to marketing) and include implementation information on Form FDA 356h.

In addition, please submit the final content of labeling (21 CFR 601.14) in SPL format via the FDA automated drug registration and listing system, (eLIST) as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

You may submit two draft copies of the proposed introductory advertising and promotional labeling with Form FDA 2253 to the Advertising and Promotional Labeling Branch at the following address:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Ave.
WO71-G112
Silver Spring, MD 20993-0002

You must submit copies of your final advertising and promotional labeling at the time of initial dissemination or publication, accompanied by Form FDA 2253 (21 CFR 601.12(f)(4)).

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence or substantial clinical experience to support such claims (21 CFR 202.1(e)(6)).

ADVERSE EVENT REPORTING

You must submit adverse experience reports in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80), and you must submit distribution reports as described in 21 CFR 600.81. For information on adverse experience reporting, please refer to the guidance for industry *Providing Submissions in Electronic Format —Postmarketing Safety Reports for Vaccines* at <http://www.fda.gov/forindustry/electronic submissions gateway/ucm387293.htm>. For information on distribution reporting, please refer to the guidance for industry *Electronic Submission of Lot Distribution Reports* at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Post-MarketActivities/LotReleases/ucm061966.htm>

TROPICAL DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a tropical disease priority review voucher, as provided under section 524 of the FDCA. This voucher entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. This priority review voucher may be transferred by you to another sponsor of a human drug or biologic application. When redeeming this priority review voucher, you should refer to this letter as an official record of the voucher. If the voucher is transferred, the sponsor to whom the voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the voucher was transferred. In addition, this priority review voucher has been assigned a tracking number, PRV 125597. All correspondences related to this voucher should refer to this tracking number. For additional information regarding the priority review voucher, see FDA's guidance, *Tropical Disease Priority Review Vouchers*, at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080599.pdf>.

PEDIATRIC REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 2 years because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group **and** is not likely to be used in a substantial number of pediatric patients in this group.

We are deferring submission of your pediatric study for ages 2 years to 18 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required postmarketing study. The status of this postmarketing study must be reported according to 21 CFR 601.28 and section 505B(a)(3)(B) of the FDCA. In addition, section 506B of the FDCA and 21 CFR 601.70 require you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

Label your annual report as an “**Annual Status Report of Postmarketing Study Requirement/Commitments**” and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements under section 506B of the FDCA are released or fulfilled. This required study is listed below:

1. Deferred pediatric study (PXVX-VC-200-006) under PREA for active immunization against disease caused by *V. cholerae* serogroup O1 in pediatric patients ages 2 years to less than 18 years traveling to cholera-affected areas. This study will evaluate the safety and immunogenicity of VAXCHORA in this age group.

Final Protocol Submission: December 31, 2016

Study Completion: December 31, 2018

Final Report Submission: June 30, 2019

Submit the protocol to your IND 15010, with a cross-reference letter to this BLA 125597 explaining that this protocol was submitted to the IND.

Submit final study reports to this BLA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated as:

- **Required Pediatric Assessment(s)**

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We acknowledge your written commitment as described in your letter of May 11, 2016, as outlined below:

2. To establish a pregnancy registry for VAXCHORA in the United States to prospectively collect data on spontaneously reported exposures to VAXCHORA occurring within 28 days prior to the last menstrual period or at any time during pregnancy. You will submit annual reports as well as a 5-year summary report, after which you will continue enrolling patients in the registry and submitting annual reports pending CBER review of the reports and determination that the registry can be discontinued.

Final Protocol Submission: July 1, 2016

Study Completion: September 1, 2021

Final Report Submission: September 1, 2022

Please submit clinical protocols to your IND 15010, and a cross-reference letter to this BLA 125597 explaining that this protocol was submitted to the IND.

If the information in the final study report supports a change in the labeling, the final study report must be submitted as a supplement. Supplements in support of labeling changes based on a postmarketing study report may be subject to a user fee. Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Commitment – Correspondence**
- **Postmarketing Commitment – Final Study Report**
- **Supplement contains Postmarketing Commitment – Final Study Report**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. Label your annual report as an **Annual Status Report of Postmarketing Requirements/Commitments** and submit it to the FDA each year within 60 calendar days of the anniversary date of this letter until all Requirements and Commitments subject to the reporting requirements of section 506B of the FDCA are fulfilled or released. The status report for each study should include:

- the sequential number for each study as shown in this letter;
- information to identify and describe the postmarketing commitment;
- the original schedule for the commitment;
- the status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted); and,
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment).

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/default.htm>.

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biological products qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the

enrollment instructions and program description details at
<http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST APPROVAL FEEDBACK MEETING

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, please contact the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V (“the Program”). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first cycle actions include: approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review committee. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review committee will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

Sincerely yours,

Mary A. Malarkey
Director
Office of Compliance and
Biologics Quality
Center for Biologics
Evaluation and Research

Marion F. Gruber, Ph.D.
Director
Office of Vaccines
Research and Review
Center for Biologics
Evaluation and Research

Attachment: Approved Final Draft Labeling